

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Cheng Hwang et al.	Art Unit	: 1617
Serial No.	: 10/721,118	Examiner	: Gina C Yu
Filed	: November 25, 2003	Conf. No.	: 6141
Title	: REDUCTION OF HAIR GROWTH		

**Mail Stop Amendment**

Commissioner for Patents

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REPLY TO ACTION OF NOVEMBER 30, 2007

In reply to the Office Action of November 30, 2007, Applicants submit the following remarks.

Claims 1, 2, 4, 8, and 29-45 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Billoni et al., Acta Derm Venereol 2000; 80: 329-334 ("Billoni") in view of Monneret et al., J. of Immun., 2002; 168: 3563-69 ("Monneret"). Applicants respectfully request that the rejection be reconsidered and withdrawn.

Applicants discovered that hair growth can be reduced by topical application of a composition containing an agonist of the receptor ("DP receptor") for prostogladin-D2 ("PGD<sub>2</sub>"). Applicants provided test data in the application demonstrating the utility of the invention. For example, the species elected by applicants (15-deoxy- $\Delta^{12,14}$ -PGD<sub>2</sub>) reduced human hair follicle growth by over 90%. See Table III on page 12 of the application.

Billoni and Monneret do not relate to the DP receptor but rather to a different receptor called PPAR $\gamma$ . According to the Examiner, Billoni teaches that ligands that bind to PPAR $\gamma$  can be used to reduce hair growth, and Monneret teaches that 15-deoxy- $\Delta^{12,14}$ -PGD<sub>2</sub> is a ligand that binds to PPAR $\gamma$ . Applicants disagree with this reasoning because Billoni does not teach that ligands that bind to PPAR $\gamma$  can be used to reduce hair growth.

Billoni begins by describing the three identified PPAR receptors and the roles served by each. Specifically, Billoni explains (at 329, citation omitted):

PPAR $\alpha$  is expressed preferentially in the liver and tissues with high fatty acid catabolism. It is involved in the fatty acid degradation and xenobiotic detoxification pathways. PPAR $\alpha$  can also stimulate target gene expression in response to diverse signals, including hypolipidemic drugs of the fibrate class.

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Recently, leukotriene B4 (LTB4) was identified as one of the natural ligands of PPAR $\alpha$ , therefore suggesting an additional role of the latter isoform in the inflammatory response. PPAR $\delta$  (also called  $\beta$  or NUC1) is ubiquitously expressed in human tissues, although its biological function and ligand(s) are still unknown. PPAR $\gamma$  is considered to be one of the key actors of the adipocyte differentiation process and its natural ligand 15-deoxy-D<sup>12,14</sup> prostaglandin J2 is a potent adipogenesis inducer. Thiazolidinedione-derived antidiabetics also bind to and activate PPAR $\gamma$ , leading to adipocyte differentiation and *in vivo* reduction in circulating lipid levels.

The quoted passage makes clear that each PPAR receptor has a distinct role in the body. PPAR $\alpha$  is “involved in fatty acid degradation and xenobiotic detoxification pathways”, and PPAR $\gamma$  is “one of the key actors of the adipocyte differentiation process.”

Billoni subsequently describes experiments establishing that the three PPAR receptors are present in hair follicles. Billoni also tests a ligand (clofibrate) for PPAR $\alpha$  for its effect on hair follicles and reports (at 333):

[Two] effects were observed in the whole-organ culture system: while high clofibrate concentration ( $10^{-6}$ ) led to cessation of hair follicle growth, low clofibrate concentrations ( $10^{-10}$  M- $10^{-8}$  M) enhanced the *in vitro* survival of human hair follicles. This effect on survival suggests that clofibrate may have a beneficial effect on hair growth, albeit within a narrow concentration window. The cause of hair growth cessation observed with  $10^{-6}$  M clofibrate remains obscure

Thus, clofibrate increased hair follicle growth (Billoni's implicit objective) at low concentration but reduced hair follicle growth at high concentration.

Billoni goes on to summarize what is known about lipid metabolism and hair growth and concludes (at 333, emphasis added):

Although these effects on human hair have been known for a long time, the putative direct effect of these agents on the hair cycle remains to be demonstrated. Taken together these clinical studies clearly demonstrate that an unbalanced lipid metabolism can lead to an alteration of the human hair cycle. We can hypothesize from our results that this alteration in the hair cycle might be at least partially due to altered PPAR-controlled pathways. This could be confirmed by using ligands other than clofibrate which are specific for the 2 other PPARs ( $\delta$  and  $\gamma$ ) expressed in the human hair follicle.

Billoni “hypothesize[s]” that the hair growth cycle “might be” effected by alteration of PPAR-controlled pathways. Billoni then concludes that ligands specific for PPAR $\gamma$  should be tested to investigate the hypothesis further.

As a practical matter, Billoni is nothing more than an invitation to conduct further research into whether ligands for PPAR $\gamma$  can effect hair growth. Billoni hypothesizes that such ligands might effect hair growth, but does not even speculate on whether that effect will be increased hair growth, reduced hair growth, or a mixed effect. In fact, Billoni seems puzzled by the mixed effect achieved with clofibrate, a ligand for a different PPAR receptor, PPAR $\alpha$ . Billoni’s emphasis on the need for further experimental work is not surprising, since the biology of hair growth is complex.

Monneret does not concern hair growth.

The framework for a 35 U.S.C. § 103(a) analysis was provided by the Federal Circuit in In re Vaeck, 947 F.2d 488, 493 (1991):

A proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should... carry out the claimed process; and (2) whether the prior art would also have revealed that in so... carrying out, those of ordinary skill in the art would have a reasonable expectation of success.

The Federal Circuit has cautioned that the “reasonable expectation of success” prong of the analysis cannot be based on hindsight knowledge that an inventor subsequently successfully used the claimed method. For example, in Life Technologies, Inv. v. Clontech Laboratories, Inc., 224 F.3d 1320, 1326 (2000) the Court explained (citations omitted):

That the inventors were ultimately successful is irrelevant to whether a person of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. The Court’s finding to the contrary represents impermissible use of hindsight -- using the inventors’ success as evidence that the success would have been expected.

Billoni and Monneret do not come close to meeting these standards. At most, Billoni is inviting research into the effect of ligands of PPAR $\gamma$  on hair growth, but provides no reasonable expectation that such ligands actually can be used to reduce hair growth. As discussed above, Billoni conducted no testing with regard to ligands of PPAR $\gamma$ , only “hypothesizes” that ligands

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of PPAR $\gamma$  might alter the hair growth cycle, and plainly does not know (if such alteration is possible) whether this will lead to an increase or a reduction in hair growth.

Thus, applicants request that the 35 U.S.C. § 103(a) rejection be withdrawn.

Applicants submit that the claims are in condition for allowance and such action is respectfully requested.

Please apply the \$460.00 Petition for Extension of Time fee and any other charges or credits to deposit account 06-1050, referencing attorney docket no. 00216-654001.

Respectfully submitted,

Date: April 7, 2008

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